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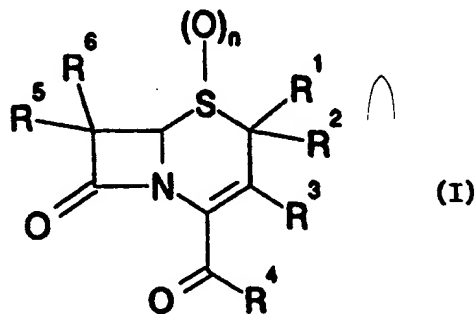
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(54) Title: USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS

(57) Abstract

The present invention relates to the use of known cephem derivatives of formula (I), wherein n is zero, one or two; R¹ is hydrogen or an organic radical, R² represents halo or an organic radical or R¹ and R² taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic group; R³ represents R² as defined above or an organic radical, R⁴ is either R¹ or an organic group, R⁵ is either R¹ as defined above or halo or C₁-C₆ alkoxy, C₁-C₆ alkylthio or C₁-C₆ acylamino; R⁶ is R² as defined above or an organic group, or pharmaceutically acceptable salt thereof.



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"USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS"

The present invention relates to the use of cephem derivatives as anti-metastatic agents.

5 As known, malignancy of cancer is mainly due to metastasis. Because therapy usually fails to destroy multiple secondary tumor, their uncontrolled growth leads to death of patients. Only very few patients die from complications directly arising from primary tumor.

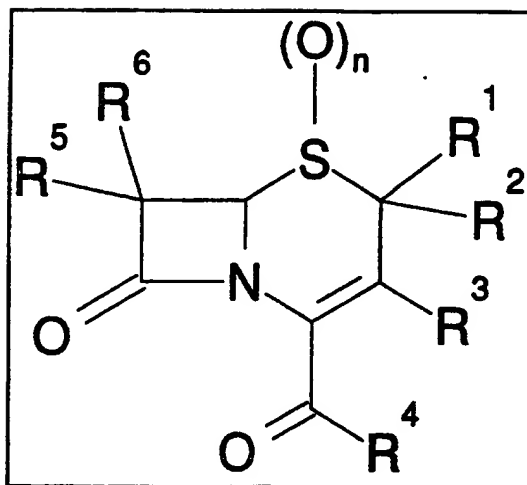
10 Accordingly, there is a need in therapy of drugs able to prevent and/or block the metastatic spread.

Several cephem derivatives were described as having elastase inhibiting activity and can be used in the treatment of inflammatory and degenerative diseases
15 caused by proteolytic enzymes in mammals including humans.

Now we have found that a selected class of compounds previously disclosed can prevent and/or block the metastatic spread of tumors in mammals, including
20 humans.

Accordingly one object of the present invention is the use of a compound of formula (I)

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wherein n is zero, one or two;

R¹ is hydrogen or an optionally substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, or C₇-C₁₄ aralkyl, C₈-C₁₄ aralkenyl, C₈-C₁₄ aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl, (heterocyclyl)alkenyl;

R² represents an atom or group selected from the following:

- (1) halogen
- (2) R¹ as defined above
- (3) an ether OR¹ wherein R¹ is as defined above
- (4) a thioether, sulfoxide or sulphone -S(O)_nR¹ wherein n and R¹ are as defined above
- (5) acyloxy -OC(O)R¹ wherein R¹ is as defined above;
- (6) sulphonyloxy -OS(O)₂R¹ wherein R¹ is as defined

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above;

or R¹ and R² taken together form a methylene group of formula =CHR¹ or =CH-CO₂R¹ or =CH-COR¹ wherein R¹ is as defined above; or R¹ and R² taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclyl group;

R³ represents one of the following:

- (1) R² as defined above
- (2) an acyl group -C(O)R¹, -C(O)OR¹ or -CO₂H wherein R¹ as defined above
- (3) an oxymethyl group -CH₂-OR¹ wherein R¹ is as defined above
- (4) a thiomethyl group or a derivative thereof of formula -CH₂S(O)_nR¹ wherein n and R¹ are as defined above
- (5) an acyloxymethyl group -CH₂OC(O)R¹ wherein R¹ is as defined above or a -CH₂O-R⁷ wherein R⁷ is a mono, di- or tripeptide composed of D or L α-aminoacids chosen from Ala, Gly, Val, Leu, Ile, Phe and with the terminal amino group either free or protected as an amide -NHCOR¹ or sulfonamide -NHSO₂R¹ wherein R¹ is as defined above
- (6) an acylthiomethyl group -CH₂SC(O)R¹ wherein R¹ is as defined above
- (7) a sulphonyloxymethyl group -CH₂-OSO₂R¹ wherein R¹ is as defined above

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- (8) a group of formula $-\text{CH}_2-\text{Z}-\text{NR}^1\text{R}^8$ wherein Z is a bond, $-\text{O}-\text{C}(\text{O})-$ or $-\text{OS}(\text{O})_2-$, R^1 is as defined above and R^8 , being the same or different, is as defined above for R^1 ; or R^1 and R^8 taken together with the nitrogen atom to which they are attached represent a heterocyclic ring;
- (9) ammoniomethyl $-\text{CH}_2\text{N}^+\text{R}^1\text{R}^8\text{R}^9$ wherein R^1 and R^8 are as defined above and R^9 , being the same or different, is as defined for R^1 ; or R^1 is alkyl and R^8 and R^9 together with the nitrogen atom to which they are attached represent a heterocyclic ring;

R^4 is either:

- (1) a group R^1 wherein R^1 is as defined above
- (2) a group OR^1 wherein R^1 is as defined above
- (3) a group SR^1 wherein R^1 is as defined above
- (4) a group NR^1R^5 wherein R^1 and R^5 are as defined above;

R^5 is either R^1 as defined above or halogen or C_1-C_6 alkoxy, C_1-C_6 alkylthio or C_1-C_6 acylamino;

R^6 is a group selected from the following:

- (1) R^2 as defined above
- (2) a group of formula $-\text{Z}-\text{N}(\text{R}^1)\text{R}^8$ wherein Z, R^1 and R^8 are as defined above
- (3) a group of formula $-\text{NR}^8\text{C}(\text{O})\text{R}^1$ wherein R^1 and R^8 are as defined above, or R^1 and R^8 taken together with

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the aminocarbonyl group to which they are attached constitute a heterocyclic ring

(4) an acylamino group $-NHR^7$ wherein R^7 is as defined above

5 (5) an ammonio group $-N^+R^1R^8R^9$ wherein R^1 , R^8 and R^9 are as defined above;

or R^5 and R^6 taken together with the C-7 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic ring;

10 or R^5 and R^6 taken together constitute a methylene group of formula $=CHR^1$, $=CH-CO-R^1$ or $=CH-SO_2R^1$ wherein R^1 is as defined above

or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in preventing and/or treating the metastatic spread of tumors.

15 A further object the present invention is to provide a compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in preventing and/or treating the metastatic spread of tumors.

20

The C_1-C_{12} alkyl group is a straight or branched alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and so on.

25 The C_2-C_{12} alkenyl group is a straight or branched alkenyl group such as vinyl, allyl, crotyl,

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2-methyl-1-propenyl, 1-methyl-1-propenyl, butenyl, pentenyl and so on.

The C_2-C_{12} alkynyl group is a straight or branched alkynyl group such as ethynyl, propargyl, 1-propynyl, 1-butynyl, 2-butynyl and so on.

The C_6-C_{10} aryl group is a monocyclic or bicyclic aromatic

hydrocarbon group of 6 to 10 carbon atoms, such as phenyl and naphthyl.

10 The C_3-C_6 cycloalkyl group is a saturated carbocyclic group of 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

The C_5-C_8 cycloalkenyl group is an unsaturated carbocyclic group such as cyclopentenyl, cyclohexenyl and so on.

15 The C_7-C_{14} aralkyl group is an alkyl group of 1 to 4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aralkyl groups are benzyl, phenylethyl and naphthylmethyl.

20 The C_8-C_{14} aralkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aralkenyl groups are styryl, 2-phenyl-1-propenyl, 3-phenyl-2-butenyl, 2-naphthylethenyl and so on.

25 The C_8-C_{14} aralkynyl group is an alkynyl group of 2 to

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4 carbon atoms linked to a monocyclic or bicyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aralkynyl groups are 2-phenylethynyl, 2-naphtylethynyl and so on.

5 The (cycloalkyl)alkyl group is an alkyl group of 1 to 4 carbon atoms linked to a cycloalkyl group.

The (cycloalkyl)alkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a cycloalkyl group or to an aryl group.

10 The heterocyclyl group is a 3- to 6-membered , saturated or unsaturated heterocyclyl ring, containing at least one heteroatom selected from O, S and N, which is optionally fused to a second 5- or 6-membered , saturated or unsaturated heterocyclyl group or to a
15 cycloalkyl group or to an aryl group.

In particular, the heterocyclyl group may be for example a tetrazole, thiadiazole, pyrrole, triazole, imidazole, oxazole, thiophene, pyridine, pyrazine, triazine, morpholine and the like.

20 The (heterocyclyl)alkyl group is an alkyl group of 1 to 4 carbon atoms linked to a heterocyclyl group.

The (heterocyclyl)alkenyl group is an alkenyl group of 2 to 4 carbon atoms linked to a heterocyclic group.

The term halogen (or halo) preferably encompasses
25 fluorine, chlorine or bromine.

The C₁-C₆ alkoxy group is a straight or branched alkylthio group such as methoxy, ethoxy, n-propoxy,

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isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, n-hexyloxy and so on.

The C₁-C₆ alkylthio group is a straight or branched alkoxy group such as methylthio, ethylthio, 5 n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-pentylthio, n-hexylthio and so on.

The C₁-C₆ acylamino group is a straight or branched acylamino group such as formamido, acetamido, 10 propionamido, pivalamido and so on.

The above said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, aralkenyl, aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl, (heterocyclyl)alkenyl, alkoxy, 15 alkylthio, acylamino groups can be either unsubstituted or substituted by one or more substituents selected from the following ones:

- halo (i.e., fluoro, bromo, chloro or iodo);
- hydroxy or oxo;
- 20 - nitro;
- azido;
- mercapto (-SH);
- amino (i.e., -NH₂, or -NHR' or -NR'R'') wherein R' and R'', which are the same or different, are C₁-C₁₂ 25 straight or branched alkyl or phenyl or benzyl;
- formyl (i.e., -CHO);

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- cyano;
- carboxy(alkyl) (i.e., $(CH_2)_tCOOH$ or $(CH_2)_tCOOR'$)
wherein R' is as defined above and t is 0, 1, 2 or 3;
- sulpho (i.e., $-SO_3H$);
- 5 - acyl (i.e., $-C(O)R'$) wherein R' is as defined above
or trifluoroacetyl (i.e., $-C(O)CF_3$);
- carbamoyl (i.e., $-CONH_2$); N-methylcarbamoyl (i.e.,
 $-CONHCH_3$) or N-carboxymethylcarbamoyl (i.e.,
 $-CONHCH_2COOH$);
- 10 - carbamoyloxy (i.e., $-OCONH_2$);
- acyloxy (i.e., $-OC(O)R'$) wherein R' is as defined
above or formyloxy (i.e., $-OC(O)H$);
- alkoxycarbonyl or benzyloxycarbonyl (i.e., $-C(O)OR'$)
wherein R' is as defined above;
- 15 - alkoxycarbonyloxy or benzyloxycarbonyloxy (i.e.,
 $-OC(O)OR'$) wherein R' is as defined above;
- alkoxy, phenoxy or benzyloxy (i.e., $-OR'$) wherein R'
is as defined above;
- alkylthio, phenylthio or benzylthio (i.e., $-SR'$)
- 20 wherein R' is as defined above;
- alkylsulphinyl, phenylsulphinyl or benzylsulphinyl
(i.e., $-S(O)R'$) wherein R' is as defined above;
- alkylsulphonyl, phenylsulphonyl or benzylsulphonyl
(i.e., $-S(O)_2R'$) wherein R' is as defined above;
- 25 - acylamino (i.e., $-NHC(O)R'''$ or $-NHC(O)OR'''$) wherein
 R''' is C_1 - C_{12} straight or branched alkyl, phenyl,
benzyl, CH_2CH_2COOH or $CH_2CH_2CH_2COOH$;

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- sulphonamido (i.e., $\text{-NHSO}_2\text{R}'$) wherein R' is as defined above;
- guanidino (i.e., -NHC(=NH)NH_2);
- $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl or alkynyl;
- 5 - $\text{C}_3\text{-C}_6$ cycloalkyl;
- phenyl
- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl,
- 10 cyanomethyl, carboxymethyl, sulphomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl, $\text{C}_1\text{-C}_4$ alkoxy carbonylmethyl, guanidinomethyl.

The carboxyl-protecting group may, for example, be a lower alkyl group such as methyl, ethyl, propyl, isopropyl or tert-butyl; a halogenated lower alkyl

15 group such as a 2,2,2-trichloroethyl or a 2,2,2-trifluoroethyl; a lower alkanoyloxyalkyl group such as acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, 1-acetoxyethyl, 1-propionyloxyethyl;

20 a lower alkoxy carbonyloxyalkyl group such as 1-(methoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl, 1-(isopropoxycarbonyloxy)ethyl; a lower alkenyl group such as 2-propenyl, 2-chloro-2-propenyl,

25 3-methoxycarbonyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, cinnamyl; an aralkyl group such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl,

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p-nitrobenzyl, benzhydryl, bis(p-methoxyphenyl)methyl;
a (5-substituted 2-oxo-1,3-dioxol-4-yl)methyl group
such as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl; a lower
alkylsilyl group such as trimethylsilyl,
5 tert-butyldimethylsilyl, tert-butyldiphenylsilyl,
triphenylsilyl; or an indanyl group; a phthalidyl group;
a pyranyl group; a methoxymethyl or methylthiomethyl
group; a 2-methoxyethoxymethyl group. Particularly
preferred are a tert-butyl group, a p-nitrobenzyl
10 group, a p-methoxybenzyl group, a benzhydryl group, a
tert-butyldimethylsilyl, tert-butyldiphenylsilyl group
or a propenyl group.

The amino, hydroxy or mercapto protecting groups
possibly present may be those usually employed in the
15 chemistry of penicillins and cephalosporins for this
kind of functions. They may be, for instance,
optionally substituted, especially halo-substituted,
acyl groups, e.g. acetyl, monochloroacetyl,
dichloroacetyl, trifluoroacetyl, benzoyl or
20 p-bromophenacyl; triarylmethyl groups, e.g.
triphenylmethyl; silyl groups, in particular
trimethylsilyl, dimethyl-tert-butylysilyl,
diphenyl-tert-butylysilyl; or also groups such as
tert-butoxycarbonyl, p-nitrobenzyloxycarbonyl,
25 2,2,2-trichloroethoxycarbonyl, benzyl and pyranyl.
Preferred protecting groups of the hydroxy function are
p-nitrobenzyloxycarbonyl; allyloxycarbonyl;

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dimethyl-tert-butylsilyl; diphenyl-tert-butylsilyl;
trimethylsilyl; 2,2,2-trichloroethoxycarbonyl; benzyl;
dimethoxybenzyl; p-methoxybenzyloxycarbonyl;
p-bromophenacyl; triphenylmethyl, pyranyl,
5 methoxymethyl, benzhydryl, 2-methoxyethoxymethyl,
formyl, acetyl, trichloroacetyl.

As already said, the invention includes within its
scope

the salts of those compounds of formula (I) that have
10 salt-forming groups, especially the salts of the
compounds having a carboxylic group, a basic group
(e.g. an amino or guanidino group), or a quaternary
ammonium group. The salts are especially
physiologically tolerable salts, for example alkali
15 metal and alkaline earth metal salts (e.g. sodium,
potassium, lithium, calcium and magnesium salts),
ammonium salts and salts with an appropriate organic
amine or amino acid (e.g. arginine, procaine salts),
and the addition salts formed with suitable organic or
20 inorganic acids, for example hydrochloric acid,
sulphuric acid, carboxylic and sulphonc organic acids
(e.g. acetic, trifluoroacetic, p-toluensulphonic acid).
Some compounds of formula (I) which contain a
carboxylate and an ammonium group may exist as
25 zwitterions; such salts are also part of the present
invention.

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The present invention encompasses all the possible stereoisomers as well as their racemic or optically active mixtures.

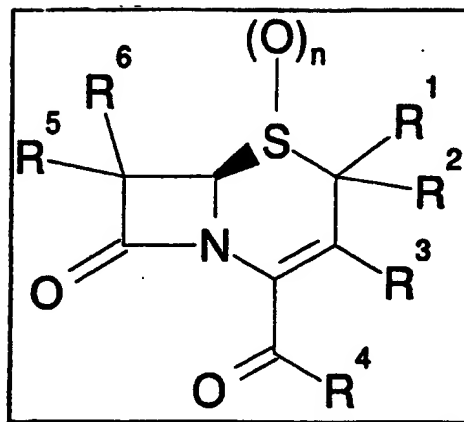
Furthermore, physiologically hydrolyzable esters, hydrates and solvates of compounds of formula (I) are included within the scope of the present invention.

The physiologically hydrolyzable esters of the compounds (I) may include, for example, methoxycarbonylmethyl, 1-methoxycarbonyloxy-1-ethyl, indanyl, phthalidyl, methoxymethyl, pivaloyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl or 5-methyl-2-oxo-1,3-dioxolan-4-yl esters, and other physiologically hydrolyzable esters which have been widely used in the technical fields of penicilin and cephalosporin antibiotics: more preferably, methoxycarbonyloxymethyl, 1-methoxycarbonyloxy-1-ethyl, methoxymethyl or pivaloyloxymethyl; and most preferably, methoxycarbonyloxymethyl or methoxymethyl.

Typical solvates of the cephalosporin compounds of formula(I) may include solvates with water miscible solvents, e.g. methanol, ethanol, acetone or acetonitrile or acetonitrile; and more preferably, ethanol.

Preferred compounds of formula (I), according to the invention, are the compounds of the formula (Ia)

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wherein n , R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 , are as defined above, and the pharmaceutically acceptable salts thereof. Examples of compounds according to the present invention are the following:

- 5 1) (6R,7S)-2-(2,2-Dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 2) 2-Benzoyl-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 10 3) 2-(2,2-Dimethyl-propionyl)-7-methoxy-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 15 4) 2-Benzoyl-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 20 5) 2-Benzoyl-7-methoxy-3-methyl-4-(1-methyl-1H-

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- tetrazol-5-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 6) 2-(2,2-Dimethyl-propionyl)-7-methoxy-3-methyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 5 7) 2-(2,2-Dimethyl-propionyl)-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 10 8) 2-Benzoyl-7-methoxy-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 15 9) 7-Allyl-2-benzoyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 20 10) 7-Allyl-2-(2,2-dimethyl-propionyl)-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 25 11) 3-(6-Hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanylmethyl)-7-methoxy-5,5-dioxo-2-(pyrrolidine-1-carbonyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 12) 1-(3-Acetoxymethyl-7-methoxy-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-2-carbonyl)pyrrolidine-2-

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carboxilic acid

- 13) 1-[3-Acetoxymethyl-5,5,8-trioxo-7-(2,2,2-trifluoro-
acetamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-
carbonyl]-pyrrolidine-2-carboxilic acid
- 5 14) 1-(7-Benzoylamino-3-methyl-5,5,8-trioxo-5-thia-1-
aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)-pyrrolidine-
2-carboxylic acid
- 15) 3-Methyl-5,5,8-trioxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-
10 benzyl ester
- 16) 2-Benzoyl-7-ethylsulfanyl-4-(5-methyl-
[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-
[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-
1-aza-bicyclo[4.2.0]oct-2-en-8-one
- 15 17) 2-Benzoyl-7-ethylsulfanyl-3-methyl-4-(5-methyl-
[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-en-8-one
- 18) 3-(1-Methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-
trioxo-7-(2,2,2-trifluoro-acetylamino)-5-thia-1-aza-
20 bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-
benzyl ester
- 19) 2-Acetylamino-3-[7-methoxy-3-(1-methyl-1H-tetrazol-
5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic
25 acid
- 20) 2-Acetylamino-3-[7-allyl-3-(1-methyl-1H-tetrazol-5-
ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-

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bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-propionic acid

and the pharmaceutically acceptable salts thereof.

Cephems of formula (I) defined under the present
5 invention are known compounds or can be prepared from known compounds by known methodologies.

For example, suitable methods for the preparation of the claimed compounds can be found in the following bibliografic references, listed according to the site
10 of functionalization of the cephem nucleus:

2-substituted cephems: Nouveau Journal de Chimie 1, 85 (1977); Synthetic Communations 15, 681 (1985); Chem. Pharm. Bull. 31, 1482 (1983); Bull. Chem. Soc. Jpn. 56, 2185 (1983); Tetrahedon Letters 21, 1293, (1980); J. Org. Chem. 44, 811 (1979); Tetrahedron Letters 4751 (1978); J. Am. Chem. Soc. 100, 1886 (1978); J. Chem. Soc. Perkin I 2298 (1977); Tetrahedron Letters 3611 (1977); J. Chem. Soc. Chem. Comm. 671 (1973); Tetrahedron Letters 3717 (1972); US 3.660.395; Eur. J. Med. Chem. 24, 599 (1989); J. Med. Chem. 14, 420 (1971); J. Med. Chem. 14, 426 (1971); Heterocycles 29, 1107 (1989); J. Med. Chem. 27, 1225 (1984).

3-substituted cephems: Heterocycles 24, 1653 (1986); J. Chem. Soc. Perkin I 1361 (1991); SynLett 389 (1990);
25 SynLett 391 (1990); J. Org. Chem. 55, 5833 (1990); Tetrahedron Letters 31, 3389 (1983); Tetrahedron 41, 2025 (1985); Chem. Pharm. Bull. 33, 5534 (1985); J.

- 18 -

- Chem. Soc. Perkin I 2281 (1983); J. Org. Chem. 53, 983 (1988); Gazz. Chim. II. 115, 169 (1985); Tetrahedron 39, 461 (1983); J. Antibiotics 39, 380 (1986); J. Am. Chem. Soc. 108, 1685 (1986); J. Chem. Soc. Chem. Comm. 1012 (1974); Chem. Pharm. Bull. 28, 2116 (1980); Gazz. Chim. IC 110, 519 (1980); Phil. Trans. R. Soc. Lond. B 289, 173 (1980); Chem. Pharm. Bull. 28, 62 (1980); J. Antibiotics 37, 1441 (1984); Tetrahedon Letters 29, 6043 (1988); Tetrahedron Letters 29, 5739 (1988); Heterocycles 1799 (1986); J. Org. Chem. 54, 5828 (1989); J. Antibiotics 42, 159 (1989); Heterocycles 28, 657 (1989); SynLett 888 (1991); J. Antibiotics 43, 533 (1990), Eur. J. Med. Chem. 27, 875 (1992).
- 4-substituted cepheims: Tetrahedron Letters 52, 5219 (1978); Tetrahedron Letters 33, 2915 (1977); J. Org. Chem. 51, 4723 (1986); Synthesis 52 (1986); J. Org. Chem. 35, 2429 (1970); J. Org. Chem. 35, 2430 (1970); US 4992-541-A; EP 0124001-A2; EP 0267723-A2; US 4.547.371; J. Med. Chem. 33, 2522 (1990); Tetrahedron Letters 32, 6207 (1991); Eur. J. Med. Chem. 27, 875 (1992), J. Med. Chem. 20, 173 (1977); J. Med. Chem. 15, 1172 (1972); US 5.077.286; PCT WO 89/10926.
- 7-substituted cephem: J. Org. Chem. 43, 3788 (1978); J. Org. Chem. 42, 2960 (1977); J. Org. Chem. 42, 3972 (1977); Tetrahedron Letters 1303 (1976); J. Med. Chem. 25, 457 (1982); Tetrahedron Letters 16, 1441 (1979); J. Chem Soc. Chem. Comm. 276 (1988); J. Chem. Soc. Perkin

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I 635 (1987); J. Org. Chem. 54, 3907 (1989); J. Antibiotics 52, 159 (1989); Tetrahedron Letters 30, 2375 (1989); Tetrahedron Letters 30, 2379 (1989) Thetrahedron Letters 375 (1972); Tetrahedron Letters 19, 1637 (1979).

As stated above, the compounds of the invention have been found to be active as anti-metastatic agents. Accordingly, they can be used in mammals, including humans, for preventing and/or treating the metastatic spread of tumors.

The antimetastatic activity of the compounds was proved experimentally in vivo against the highly metastatic B16F10 murine melanoma. B16F10 tumor cells were maintained in vitro by serial soil. For experimental purpose, tumor cells were pretreated in vitro with 1000γ for 6 hrs, whereas control were incubated with medium. Cells were then harvested and injected intravenously into C57/Bl6 mice at the concentration of 10⁵ cells/mouse. Animals were treated intraperitoneally with the compound for 6 days at the dose of 200 mg/kg. After 22 days mice were sacrificed and the number of lung metastatic foci were counted.

Data reported in table 1 show that a representative compound of the invention, namely (6R,7S)-2-(2,2-dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-

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one (internal code FCE26238) is clearly active as antimetastatic agent. An evident reduction of the metastasis number was observed after in vitro pretreatment and after in vivo treatment. No evidence of toxicity was observed.

Table 1

Group	Treatment with FCE26238		median number of metastasis (range)
	in vitro	in vivo	
Control	-	-	20 (7-72)
	-	200 mg/kg x6	4 (2-24)
	1000 γ x 6 hrs	-	0 (0-0)
	1000 γ x 6 hrs	200 mg/kg x6	0 (0-0)

The compounds of the invention can be administered by the usual routes, for example, parenterally, e.g. by intravenous injection or infusion, intramuscularly, subcutaneously, topically or orally, intravenous injection or infusion being the preferred. The dosage depends on the age, weight and condition of the patient and on the administration route.

A suitable dosage for the compounds of the invention, e.g. FCE26238 for administration to adult humans may

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range from about 0.5 to about 300 mg per dose 1-4 times a day.

The pharmaceutical compositions of the invention may contain a compound of formula (I) or a pharmaceutically acceptable salt thereof, as the active substance, in association with one or more pharmaceutically acceptable excipients and/or carriers.

The pharmaceutical compositions of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form. For instance, solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or, preferably, they may be in the form of sterile aqueous isotonic saline solutions.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride.

In the form for topical application, e.g. creams, lotions or pastes for use in dermatological treatment, the active ingredient may be mixed with conventional oleaginous or emulsifying excipients.

The solid oral forms, e.g. tablets and capsules, may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn

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starch and potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethyl cellulose, polyvinylpyrrolidone; 5 disaggregating agents, e.g. a starch, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, for instance, lecithin, polysorbates, laurylsulphates; and, 10 in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in a known manner, for example by means of mixing, granulating, tableting, sugar-coating, or film-coating 15 processes.

An object of the invention is also to provide a method of treatment of the above mentioned pathological conditions comprising both separate and substantially contemporaneous administration of a composition 20 containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutical composition containing a different pharmaceutically active agent, typically an antitumor agent.

25 Antitumor agents that can be formulated with a compound of the invention or, alternatively, can be administered in a combined method of treatment are e.g. doxorubicin,

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daunomycin, epirubicin, idarubicin, etoposide, fluorouracil, paclitaxel, melphalan, cyclophosphamide, bleomycin, vinblastin and mitomycin or a mixture of two or more thereof.

- 5 The compounds of the invention can therefore be used in a treatment to ameliorate a cancer.

EXAMPLE A

Tablets:

		Per 10,000	
	<u>Ingredients</u>	<u>Per Tablet</u>	<u>Tablets</u>
10	1. Active ingredient Cpd of Form I	40.0 mg	400 g
	2. Corn Starch	20.0 mg	200 g
	3. Alginic acid	20.0 mg	200 g
	4. Sodium alginate	20.0 mg	200 g
15	5. Magnesium Stearate	<u>1.3 mg</u>	<u>13 g</u>
		101.3 mg	1013 g

Procedure for tablets:

- 20 Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender .
- Step 2. Add sufficient water portionwise to the blend from Step 1 with careful mixing after each

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addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

5 Step 3. The wet mass is converted to granules by passing it through an oscillating granulator using a number 8 mesh (2.38) screen.

Step 4. The wet granules are dried in an oven at 60°C until dried.

10 Step 5. The dried granules are lubricated with ingredient no. 5.

Step 6. The lubricated granules are compressed on a suitable tablet press.

Example B

Intramuscular injection:

15	<u>Ingredients</u>	<u>Per ml</u>	<u>Per liter</u>
	1. Active ingredient	10.0 mg	10 g
	Cpd of Form I		
	2. Isotonic buffer	q.s.	q.s.
	solution pH 4.0.		

20

Procedure:

Step 1. Dissolve the active ingredient in the buffer solution.

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Step 2. Aseptically filter the solution from step 1.

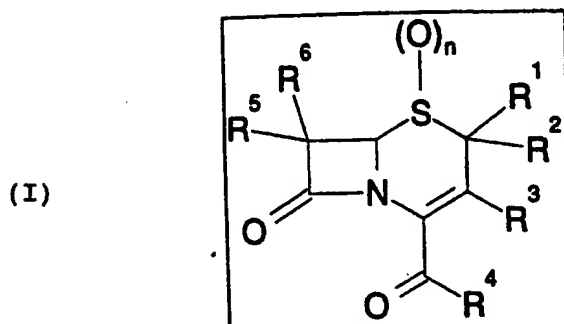
Step 3. The sterile solution is aseptically filled
into sterile ampoules

Step 4. The ampoules are sealed under aseptic
conditions

5

CLAIMS

1. The use of a compound of formula (I)



5

wherein n is zero, one or two;

R¹ is hydrogen or an optionally substituted C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, or C₇-C₁₄ aralkyl, C₈-C₁₄ aralkenyl, C₈-C₁₄ aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl, (heterocyclyl)alkenyl;

10

R² represents an atom or group selected from the following:

15

(1) halogen

(2) R¹ as defined above

(3) an ether OR¹ wherein R¹ is as defined above

(4) a thioether, sulfoxide or sulphone -S(O)_nR¹ wherein n and R¹ are as defined above

20

(5) acyloxy -OC(O)R¹ wherein R¹ is as defined above;

(6) sulphonyloxy -OS(O)₂R¹ wherein R¹ is as defined

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above;

or R¹ and R² taken together form a methylene group of formula =CHR¹ or =CH-CO₂R¹ or =CH-COR¹ wherein R¹ is as defined above; or R¹ and R² taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclyl group; R³ represents one of the following:

- (1) R² as defined above
- (2) an acyl group -C(O)R¹, -C(O)OR¹ or -CO₂H wherein R¹ as defined above
- (3) on oxymethyl group -CH₂-OR¹ wherein R¹ is as defined above
- (4) a thiomethyl group or a derivative thereof of formula -CH₂S(O)_nR¹ wherein n and R¹ are as defined above
- (5) an acyloxymethyl group -CH₂OC(O)R¹ wherein R¹ is as defined above or a -CH₂O-R⁷ wherein R⁷ is a mono, di- or tripeptide composed of D or L α-aminoacids chosen from Ala, Gly, Val, Leu, Ile, Phe and with the terminal amino group either free or protected as an amide -NHCOR¹ or sulfonamide -NHSO₂R¹ wherein R¹ is as defined above
- (6) an acylthiomethyl group -CH₂SC(O)R¹ wherein R¹ is as defined above
- (7) a sulphonyloxymethyl group -CH₂-OSO₂R¹ wherein R¹ is as defined above

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- 5 (8) a group of formula $-\text{CH}_2-\text{Z}-\text{NR}^1\text{R}^8$ wherein Z is a bond, $-\text{O}-\text{C}(\text{O})-$ or $-\text{OS}(\text{O})_2-$, R^1 is as defined above and R^8 , being the same or different, is as defined above for R^1 ; or R^1 and R^8 taken together with the nitrogen atom to which they are attached represent a heterocyclic ring;
- 10 (9) ammoniomethyl $-\text{CH}_2\text{N}^+\text{R}^1\text{R}^8\text{R}^9$ wherein R^1 and R^8 are as defined above and R^9 , being the same or different, is as defined for R^1 ; or R^1 is alkyl and R^8 and R^9 together with the nitrogen atom to which they are attached represent a heterocyclic ring;

R^4 is either:

- 15 (1) a group R^1 wherein R^1 is as defined above
- (2) a group OR^1 wherein R^1 is as defined above
- (3) a group SR^1 wherein R^1 is as defined above
- (4) a group NR^1R^5 wherein R^1 and R^8 are as defined above;

20 R^5 is either R^1 as defined above or halogen or C_1-C_6 alkoxy, C_1-C_6 alkylthio or C_1-C_6 acylamino;

R^6 is a group selected from the following:

- (1) R^2 as defined above
- (2) a group of formula $-\text{Z}-\text{N}(\text{R}^1)\text{R}^8$ wherein Z, R^1 and R^8 are as defined above
- 25 (3) a group of formula $-\text{NR}^8\text{C}(\text{O})\text{R}^1$ wherein R^1 and R^8 are as defined above, or R^1 and R^8 taken together with the amin carbonyl group to

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which they are attached constitute a heterocyclic ring

(4) an acylamino group $-NHR^7$ wherein R^7 is as defined above

5 (5) an ammonio group $-N^+R^1R^8R^9$ wherein R^1 , R^8 and R^9 are as defined above;

or R^5 and R^6 taken together with the C-7 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic ring;

10 or R^5 and R^6 taken together constitute a methylene group of formula $=CHR^1$, $=CH-CO-R^1$ or $=CH-SO_2R^1$, wherein R^1 is as defined above, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for use in preventing
15 and/or treating the metastatic spread of tumors.

2. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1 in preventing and/or treating the metastatic spread of tumors.

20 3. The use of a compound of formula (I), according to claim 1 or 2, wherein the compound is selected from

(6R,7S)-2-(2,2-dimethyl-propionyl)-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-
25 aza-bicyclo[4.2.0] oct-2-en-8-one,
2-benzoyl-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-

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- 2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 5 2-(2,2-dimethyl-propionyl)-7-methoxy-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 10 2-benzoyl-4-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanyl)-7-methoxy-3-methyl-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 2-benzoyl-7-methoxy-3-methyl-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 15 2-(2,2-dimethyl-propionyl)-7-methoxy-3-methyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 2-(2,2-dimethyl-propionyl)-7-methoxy-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 20 2-benzoyl-7-methoxy-4-(1-methyl-1H-tetrazol-5-ylsulfanyl)-3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 25 7-allyl-2-benzoyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-3-(5-methyl-[1,3,4]thiadiazol-2-

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- ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
7-allyl-2-(2,2-dimethyl-propionyl)-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-3-(5-methyl-
5 [1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
3-(6-hydroxy-2-methyl-5-oxo-2,5-dihydro-[1,2,4]triazin-3-ylsulfanylmethyl)-7-methoxy-5,5-dioxo-2-(pyrrolidine-1-carbonyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
10 1-(3-acetoxymethyl-7-methoxy-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)pyrrolidine-2-carboxylic acid,
1-[3-acetoxymethyl-5,5,8-trioxo-7-(2,2,2-trifluoro-ace tylamino)-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl]-pyrrolidine-2-carboxylic acid,
15 1-(7-benzoylamino-3-methyl-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-enane-2-carbonyl)-pyrrolidine-2-carboxylic acid,
20 3-methyl-5,5,8-trioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-carboxy-benzyl ester,
2-benzoyl-7-ethylsulfanyl-4-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-3-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-5,5-dioxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-8-one,
25

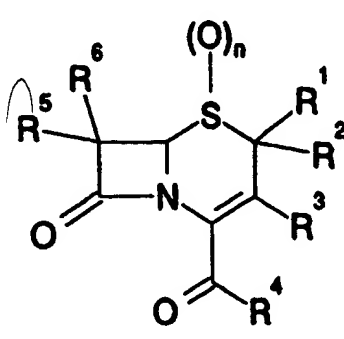
- 32 -

- 2-benzoyl-7-ethylsulfanyl-3-methyl-4-(5-methyl-
[1,3,4]thiadiazol-2-ylsulfanyl)-5,5-dioxo-5-thia-
1-aza-bicyclo[4.2.0]oct-2-en-8-one,
- 5 3-(1-methyl-1H-tetrazol-5-ylsulfanylmethyl)-5,5,8-
trioxo-7-(2,2,2-trifluoro-acetylamino)-5-thia-1-
aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid 4-
carboxy-benzyl ester,
- 10 2-acetylamino-3-[7-methoxy-3-(1-methyl-1H-
tetrazol-5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-
1-aza-bicyclo[4.2.0]oct-2-enane-2-
carbonylsulfanyl]-propionic acid,
- 15 2-acetylamino-3-[7-allyl-3-(1-methyl-1H-tetrazol-
5-ylsulfanylmethyl)-5,5,8-trioxo-5-thia-1-aza-
bicyclo[4.2.0]oct-2-enane-2-carbonylsulfanyl]-
propionic acid or a pharmaceutically acceptable
salt thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP94/02059 (22) International Filing Date: 24 June 1994 (24.06.94) (30) Priority Data: 9314562.1 14 July 1993 (14.07.93) GB (71) Applicant (for all designated States except US): PHARMACIA S.P.A. [IT/IT]; Via Robert Koch, 1.2., I-20152 Milan (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): ALPEGIANI, Marco [IT/IT]; Via Tolmezzo, 12/5, I-20132 Milan (IT). BIS-SOLINO, Pierluigi [IT/IT]; Via Roma, 36/2, I-27020 San Giorgio di Lomellina (IT). PERRONE, Ettore [IT/IT]; Via Aldo Moro, 44, I-20010 Boffalora Ticino (IT). PESENTI, Enrico [IT/IT]; Viale Visconti, 9, I-20093 Cologno Monzese (IT).		(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of receipt of the international search report: 9 March 1995 (09.03.95)
(54) Title: USE OF CEPHEM DERIVATIVES AS ANTI-METASTATIC AGENTS (57) Abstract <p>The present invention relates to the use of known cephem derivatives of formula (I), wherein n is zero, one or two; R¹ is hydrogen or an organic radical, R² represents halo or an organic radical or R¹ and R² taken together with the C-2 carbon atom of the cephem nucleus constitute a carbocyclic or heterocyclic group; R³ represents R² as defined above or an organic radical, R⁴ is either R¹ or an organic group, R⁵ is either R¹ as defined above or halo or C₁-C₆ alkoxy, C₁-C₆ alkylthio or C₁-C₆ acylamino; R⁶ is R² as defined above or an organic group, or pharmaceutically acceptable salt thereof.</p> <div style="text-align: right;">  </div> <div style="text-align: right;">(I)</div>		

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FR	France			VN	Viet Nam
GA	Gabon				

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/02059

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/00 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	GB,A,2 266 525 (MERCK & CO., INC.) 3 November 1993 see page 1, line 17 - page 1, line 28; claims 1-10	1-3
Y	--- PATENT ABSTRACTS OF JAPAN vol. 15, no. 256 (C-0845) 28 June 1991 & JP,A,03 083 987 (FUJISAWA PHARMACEUT. CO. LTD.) 9 April 1991 see abstract	1-3
A	--- EP,A,0 484 870 (BRISTOL-MYERS CO.) 13 May 1992 see claims 1-18	1-3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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